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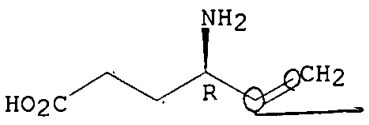
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> s vigabatrin
L1 3 VIGABATRIN

=> d 1-3

L1 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2002 ACS
RN 77162-51-7 REGISTRY
CN 5-Hexenoic acid, 4-amino-, (4R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Hexenoic acid, 4-amino-, (R)-
OTHER NAMES:
CN (-)-.gamma.-Vinyl GABA
CN **(R)-Vigabatrin**
CN **R-(-)-Vigabatrin**
CN RMI 71894
FS STEREOSEARCH
MF C6 H11 N O2
CI COM
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, DRUGPAT, DRUGUPDATES, IPA, PROMT, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (-).



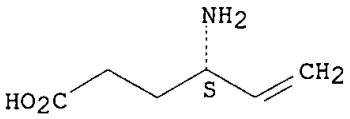
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

25 REFERENCES IN FILE CA (1967 TO DATE)
25 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L1 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2002 ACS
RN 74046-07-4 REGISTRY

CN 5-Hexenoic acid, 4-amino-, (4S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Hexenoic acid, 4-amino-, (S)-
OTHER NAMES:
CN (+)-.gamma.-Vinyl GABA
CN **(S)-Vigabatrin**
CN 4(S)-Amino-5-hexenoic acid
CN RMI 71890
CN **S-(+)-Vigabatrin**
FS STEREOSEARCH
MF C6 H11 N O2
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CSCHEM, DRUGPAT, DRUGUPDATES, IPA, PROMT, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

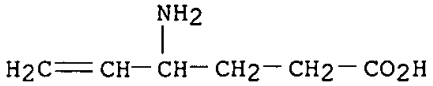
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

40 REFERENCES IN FILE CA (1967 TO DATE)
40 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L1 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2002 ACS
RN 68506-86-5 REGISTRY
CN 5-Hexenoic acid, 4-amino- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Hexenoic acid, 4-amino-, (.+-.)-
OTHER NAMES:
CN (.+-.)-.gamma.-Vinyl GABA
CN (.+-.)-4-Amino-5-hexenoic acid
CN .gamma.-Vinyl-.gamma.-aminobutyric acid
CN .gamma.-Vinyl-GABA
CN 4-Amino-5-hexenoic acid
CN MDL 71754
CN RMI 71754
CN Sabril
CN **Vigabatrin**
FS 3D CONCORD
DR 60643-86-9
MF C6 H11 N O2
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, PHAR, PHARMASEARCH, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

218 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
219 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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NEWS 2	Jan 25	BLAST(R) searching in REGISTRY available in STN on the Web
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NEWS 4	Feb 01	DKILIT now produced by FIZ Karlsruhe and has a new update frequency
NEWS 5	Feb 19	Access via Tymnet and SprintNet Eliminated Effective 3/31/02
NEWS 6	Mar 08	Gene Names now available in BIOSIS
NEWS 7	Mar 22	TOXLIT no longer available
NEWS 8	Mar 22	TRCTHERMO no longer available
NEWS 9	Mar 28	US Provisional Priorities searched with P in CA/CAplus and USPATFULL
NEWS 10	Mar 28	LIPINSKI/CALC added for property searching in REGISTRY
NEWS 11	Apr 02	PAPERCHEM no longer available on STN. Use PAPERCHEM2 instead.
NEWS 12	Apr 08	"Ask CAS" for self-help around the clock
NEWS 13	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 14	Apr 09	ZDB will be removed from STN
NEWS 15	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 16	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 17	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 18	Apr 22	Federal Research in Progress (FEDRIP) now available

NEWS EXPRESS	February 1 CURRENT WINDOWS VERSION IS V6.0d, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
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NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

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FILE 'HOME' ENTERED AT 14:50:52 ON 21 MAY 2002

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L Number	Hits	Search Text	DB	Time stamp
1	1	"5084479" .PN.	USPAT; US-PGPUB	2002/05/21 16:35
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3	5	(alanine or leucine or valine or glycine or isoleucine or tyrosine or ornithine or threonine or lysine) and (pregabalin or (pd adj "144550"))	USPAT; US-PGPUB	2002/05/21 16:36
4	80375	(alanine or leucine or valine or glycine or isoleucine or tyrosine or ornithine or threonine or lysine)	USPAT; US-PGPUB	2002/05/21 16:36
5	157	((alanine or leucine or valine or glycine or isoleucine or tyrosine or ornithine or threonine or lysine)) and baclofen	USPAT; US-PGPUB	2002/05/21 16:36
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7	62007	(alanine or leucine or valine or isoleucine or tyrosine or ornithine or threonine or lysine)	USPAT; US-PGPUB	2002/05/21 16:37
8	126	((alanine or leucine or valine or isoleucine or tyrosine or ornithine or threonine or lysine)) and baclofen	USPAT; US-PGPUB	2002/05/21 16:43
9	163	(amino adj acid) and baclofen	USPAT; US-PGPUB	2002/05/21 16:43
10	1	(amino adj acid) and stabilz?	USPAT; US-PGPUB	2002/05/21 16:44
11	6596	(amino adj acid) and stabiliz?	USPAT; US-PGPUB	2002/05/21 16:44
12	6	((amino adj acid) and stabiliz?) and baclofen	USPAT; US-PGPUB	2002/05/21 16:44
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-	1	"4126684" .pn.	USPAT; US-PGPUB	2002/05/21 10:55
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-	76029	(glutamic or aspartic or arginine or diaminoheptanoic or aminobutyric or aminovaleric or tyrosine or trptophan or methionine or norvaline or homoserine or serine or thyroxine or methyldopa or levodopa or cysteine or phenylalanine or aminopimelic)	USPAT; US-PGPUB	2002/05/21 10:59

-	114	(gabapentin or (go adj "2450") or (goe adj "2450") or neurontin or (ci adj "945") or ((aminomethyl)adj cyclohexaneacetic)) and ((glutamic or aspartic or arginine or diaminoheptanoic or aminobutyric or aminovaleric or tyrosine or trptophan or methionine or norvaline or homoserine or serine or thyroxine or methyldopa or levodopa or cysteine or phenylalanine or aminopimelic))	USPAT; US-PGPUB	2002/05/21 16:06

L17 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:545845 CAPLUS
DOCUMENT NUMBER: 129:313668
TITLE: Pharmacological analysis of the inward current produced by GABA in an identifiable giant neuron of an African giant snail (Achatina fulica Ferussac)
AUTHOR(S): Wong, Shu Ming; Zhang, Wei; Han, Xiao Yan; Salunga, Thucydides L.; Takeuchi, Hiroshi; Matsunami, Kenichi
CORPORATE SOURCE: Sch. Med., Gifu Univ., Gifu, 500-8705, Japan
SOURCE: Gifu Daigaku Igakubu Kiyo (1998), 46(3/4), 157-172
CODEN: GDIKAN; ISSN: 0072-4521
PUBLISHER: Gifu Daigaku Igakubu
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

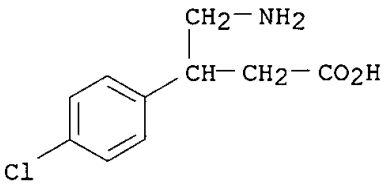
AB The pharmacol. characteristics of the excitatory GABA receptors, termed muscimol II type GABA receptors, found in a giant neuron type, V-LCDN (ventral-left cerebral distinct neuron), of an African giant snail (A. fulica), were elucidated by using the mammalian GABA and L-glutamic acid (L-Glu) agonists and related compds., and GABA antagonists, synergists and uptake inhibitor and Cl--channel blocker, under a voltage clamp condition. GABA and some of GABA agonists and related compds., ejected by brief pressure locally to the neuron examd., produced a marked inward current (Iin). The order of their potency to produce the Iin was as follows: trans-4-aminocrotonic acid (TACA) > GABA > muscimol > isoguvacine hydrochloride > 5-aminopentanoic acid and cis-4-aminocrotonic acid (CACA). Glycine and 4,5,6,7-tetrahydroisoxazolo [4,5-c]-pyridine-3-ol (THPO) produced a weak Iin. Of the compds. related to L-Glu, erythro-p-hydroxy-L-glutamic acid (erythro-L-BHGA) and threo-L-BHGA, ejected by the brief pressure, produced a marked outward current (Iout) on this neuron type. L-Glu, D-Glu, erythro-D-BHGA, and threo-D-BHGA produced an Iout, weaker than that of L-BHGA. On the other hand, (.+-.)-**baclofen**, 3-aminopropylphosphonic acid (APPA), .beta.-**alanine**, and taurine had no effect on this neuron type. The Iin values produced by GABA, TACA, isoguvacine, and CACA, ejected by the brief pressure repetitively with 5-10 min intervals, were **stable** for .gtoreq.60 min, whereas the Iin values caused by muscimol, ejected with even 15 min intervals, was markedly decreased from the 2nd trial. The dose (pressure duration)-response curves of GABA, TACA, isoguvacine, and CACA were measured by varying the pressure duration of their ejection. ED50 values of TACA and isoguvacine were comparable to that of GABA, whereas that of CACA was higher than that of GABA. Fmax value of TACA was significantly larger than that of GABA, while those of isoguvacine and CACA were significantly smaller than that of GABA. Of the GABA antagonists, synergists, uptake inhibitor and Cl--channel blocker, 5-aminopentanoic acid, pentobarbital sodium, picrotoxin, and .beta.-**alanine**, applied by perfusion, inhibited the Iin produced by GABA, whereas (-)-bicuculline methiodide, pitrazepin, diazepam, and 2-hydroxysaclofen had no effect on this Iin. The dose (pressure duration)-response curves of GABA, measured by varying the pressure duration of GABA ejection, were obsd. under 5-aminopentanoic acid, pentobarbital, or .beta.-**alanine**, and analyzed by the Lineweaver-Burke plot. It was considered that 5-aminopentanoic acid and pentobarbital non-competitively inhibited the Iin Produced by GABA, and that .beta.-**alanine** competitively inhibited this Iin. With the results mentioned above, it was concluded that the pharmacol. characteristics of the Achatina muscimol II type GABA receptors were identical to those of mammalian GABAc (GABA.rho.1) receptors, except for the effects of pentobarbital.

IT **1134-47-0**, (.+-.)-**Baclofen**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. anal. of inward current produced by GABA in identifiable

giant neuron of African giant snail)

RN 1134-47-0 CAPLUS

CN Benzenepropanoic acid, .beta.-(aminomethyl)-4-chloro- (9CI) (CA INDEX NAME)



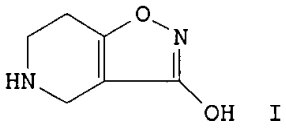
ACCESSION NUMBER: 1984:448577 CAPLUS
DOCUMENT NUMBER: 101:48577
TITLE: Synergistic **anticonvulsant** effects of **GABA**-T **inhibitors** and **glycine**
AUTHOR(S): Seiler, Nikolaus; Sarhan, Shakir
CORPORATE SOURCE: Merrell Dow Res. Inst., Strasbourg, F-67084, Fr.
SOURCE: Naunyn-Schmiedeberg's Arch. Pharmacol. (1984), 326(1), 49-57
CODEN: NSAPCC; ISSN: 0028-1298
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **anticonvulsant** effect of **inhibitors** of 4-aminobutyrate-2-oxoglutarate aminotransferase (**GABA**-T) [9037-67-6] (R/S-.gamma.-vinyl-**GABA** [68506-86-5], ethanolamine O-sulfate [926-39-6], gabaculine [59556-29-5], and aminooxyacetic acid [645-88-5]) was enhanced by 10 mmol/kg **glycine** [56-40-6] in animal seizure models which are based on a functional **GABA** deficit. Similar to **glycine** in their action, although less effective, were its close structural analogs (sarcosine [107-97-1] and N,N-dimethylglycine [1118-68-9]) and homologous .omega.-aminoacids (.beta.-alanine [107-95-9], taurine [107-35-7], .gamma.-aminobutyric acid [56-12-2], and .delta.-aminovaleric acid [660-88-8]). It is assumed that **glycine** and its structural analogs act on supraspinal **glycine** receptors as **glycine** agonists. This is the 1st example of the synergistic interaction of 2 inhibitory neuronal systems resulting in the amplification of the **anticonvulsant** effect. Combined treatments with **GABA**-T **inhibitors** and **glycine** may be of practical importance in the therapy of seizure disorders and other diseases, for which treatment with **GABA**-T **inhibitors** is considered a potentially useful therapeutic approach.

L2 ANSWER 12 OF 17 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1984:544017 CAPLUS
DOCUMENT NUMBER: 101:144017
TITLE: The amplification of the **anticonvulsant** effect of vinyl GABA (4-aminohexenoic acid) by esters of **glycine**
AUTHOR(S): Sarhan, S.; Kolb, M.; Seiler, N.
CORPORATE SOURCE: Strasbourg Cent., Merrell-Dow Res. Inst., Strasbourg, F-67084, Fr.
SOURCE: Arzneim.-Forsch. (1984), 34(6), 687-90
CODEN: ARZNAD; ISSN: 0004-4172
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **anticonvulsant** effect of vinyl **GABA** [68506-86-5] a **GABA**-T (4-aminobutyrate: 2-oxoglutarate aminotransferase) **inhibitor** with antiepileptic efficacy, can be amplified by esters of **glycine**. Among the compds. studied **glycine** tert-butyl ester [6456-74-2] was the most promising. It was effective at a lower dose and had a considerably longer duration of action than **glycine**. From the obsd. **glycine** and **glycine** tert-butyl ester levels it is evident that **glycine** tert-butyl ester is rapidly hydrolyzed within brain and other tissues. It is therefore a pro-drug of **glycine**, capable of enhancing central glycinergic activity.

L2 ANSWER 10 OF 17 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1985:571935 CAPLUS
DOCUMENT NUMBER: 103:171935
TITLE: Amplification by **glycine** of the **anticonvulsant** effect of THPO, a **GABA** uptake **inhibitor**
AUTHOR(S): Seiler, N.; Sarhan, S.; Krogsgaard-Larsen, P.; Hjeds, H.; Schousboe, A.
CORPORATE SOURCE: Merrell-Dow Res. Inst., Strasbourg, 67084, Fr.
SOURCE: Gen. Pharmacol. (1985), 16(5), 509-11
CODEN: GEPHDP; ISSN: 0306-3623
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB 4,5,6,7-Tetrahydroisoxazolo[4,5-c]pyridin-3-ol (THPO)(I) [53602-00-9], a **GABA** uptake **inhibitor**, when given in doses of up to 4 mmol/kg (i.p.) to mice, had only a marginal protective effect against seizures induced 1 h later by 3-mercaptopropionic acid (MPA). I (4 mmol/kg), when given in combination with 10 mmol **glycine** [56-40-6]/kg, protected 60% of the mice from MPA-induced convulsions. The combination of I and **glycine** delayed the onset of metrazole-induced clonic convulsions and protected 30% of the animals from seizures, although neither **glycine** nor I alone had a significant **anticonvulsant** effect against metrazole-induced seizures. Apparently, the synergistic **anticonvulsant** effects of **glycine** and GABAergic agents are independent of their mode of action: the effects of **GABA** agonists (muscimol), **GABA** -transaminase **inhibitors** (vinyl **GABA**), or an **inhibitor** of glial **GABA** uptake (I) are similarly amplified by **glycine**.

2 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:400491 CAPLUS
DOCUMENT NUMBER: 113:491
TITLE: Microionophoretic study with milacemide, a **glycine** precursor, on mammalian central nervous system cells
AUTHOR(S): Godfraind, Jean Marie
CORPORATE SOURCE: Fac. Med., UCL, Brussels, B-1200, Belg.
SOURCE: Br. J. Pharmacol. (1990), 100(1), 119-25
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of milacemide, a **glycine** precursor known to increase .gamma.-aminobutyric acid (**GABA**) and **glycine** content in the brain, and to have **anticonvulsant** properties, was tested by ionophoresis on 247 neurons situated in the cerebral cortex and in deeper structures of cats and rats anesthetized with urethane. Virtually all the neurons, either firing spontaneously or exogenously driven by the excitatory amino acids, glutamate, N-methyl-D-aspartate (NMDA), kainate and quisqualate or by acetylcholine, were reversibly depressed in a dose-dependent fashion. The same depressant effect was obsd. in animals pretreated with the monoamine oxidase B **inhibitor** deprenyl which is known to reduce milacemide metab. into glycinamide and **glycine**. I.v. administration of milacemide (10 to 100 mg kg-1) also depressed the firing induced by glutamate, NMDA and acetylcholine. When compared to **GABA**, milacemide was a weaker depressant. However, its effect could still be obsd. in the presence of the reversible GABAA antagonist, SR 95531, and thus milacemide is unlikely to act through **GABA** receptors. In addn., on cells unaffected by **glycine**, milacemide also had a depressant effect, and on cells inhibited by **glycine**, it was still capable of depressing cell firing during reversible blockade by strychnine of the **glycine** inhibitory action; thus milacemide is unlikely to act through **glycine** receptors. Simultaneous release of milacemide and **GABA** or of milacemide and **glycine**, did not show potentiation of the inhibitory amino acid action. However, the depressant effect of milacemide was additive with that of **GABA** and **glycine**. No consistent depression of glutamate-induced firing was obtained by ionophoresis of glycinamide, the first metabolite of milacemide. Thus, milacemide is a depressant agent and its depressant effect does not necessarily require its metab. into **glycine**, or its stimulator effect on the prodn. of **GABA**.

L2 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:116540 CAPLUS
DOCUMENT NUMBER: 118:116540
TITLE: **GABA**-T **inhibitors** as **anticonvulsants**: some biochemical and pharmacological properties of (S)-4-allenylGABA and a prodrug, 1-allenylputrescine
AUTHOR(S): Sarhan, S.; Casara, P.; Knoedgen, B.; Seiler, N.
CORPORATE SOURCE: Marion Merrell Dow Res. Inst., Strasbourg, 67009, Fr.
SOURCE: Mol. Neuropharmacol. (1992), 2(3), 173-80
CODEN: MOLNEO
DOCUMENT TYPE: Journal
LANGUAGE: English

AB (S)-4-Amino-5,6-heptadienoic acid (allenyl-GABA) is a selective inactivator of GABA transaminase (GABA-T). It shows many of the properties of vigabatrin, but it is more potent and in animals at biol. equiv. doses has less side-effects. Treatment of mice with allenyl-GABA enhanced GABA concns. time- and dose-dependently. At a brain GABA concn. of 4 .mu.mol/g, 50% of the mice were protected against 3-mercaptopropionic acid (MPA)-induced convulsions (oral ED50 = 60 mg/kg). Protection against pentylenetetrazole and N-methyl-DL-aspartate-induced convulsions was incomplete. Antagonism of phencyclidine-induced hyperactivity in mice was achieved at doses 100-300 mg allenyl-GABA/kg. The synergistic amplification of the **anticonvulsant** effect by **glycine** was somewhat less efficient than with **glycine**-vigabatrin combinations. After long-term treatment with small doses of allenyl-GABA, the protection against MPA-induced seizures was reduced due to down-regulation of glutamate decarboxylase, but this did not produce a neg. shift of the dose-response curve. 1-Allenylputrescine (5,6-heptadiene-1,4-diamine) is a substrate of MAO B. The compd. is transformed in vivo into 4-allenyl-GABA, and has allenyl-GABA-like biochem. and pharmacol. properties.

L2 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:523407 CAPLUS
DOCUMENT NUMBER: 129:269819
TITLE: Cellular mechanisms for felbamate, stiripentol, tiagabine, vigabatrin and zonisamide
AUTHOR(S): Monaco, Francesco
CORPORATE SOURCE: Department of Neurosciences, University of Torino, Italy
SOURCE: Current Problems in Epilepsy (1997), 12(Molecular and Cellular Targets for Antiepileptic Drugs), 207-213
CODEN: CPEPES; ISSN: 0950-4591
PUBLISHER: John Libbey & Co. Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 29 refs. (1) Vigabatrin (.gamma.-vinyl-**GABA**) (GVG) is a relatively specific irreversible **inhibitor** of **GABA**-T, the major enzyme responsible for the catabolic degrdn. of **GABA** in the mammalian CNS. Administration of GVG to lab. exptl. animals produces a prolonged inhibition of brain **GABA**-T, with a concomitant elevation in whole brain **GABA** concns., more evident in the synaptosomal pool. The results of a variety of pharmacol. studies demonstrated that GVG is effective in a no. of models in which alterations of GABAergic neurotransmission play a significant role, i.e. epilepsy, analgesia, spasticity and tardive dyskinesia. (2) The precise mechanism of action of felbamate (2-phenyl-1,3-propanediol dicarbamate) (FLB) is not known, but it specifically interacts at the strychnine-insensitive **glycine** recognition site on the NMDA receptor-ionophore complex. It also affects significantly sodium flux in vitro similar to other AEDs. Recent studies suggest a dual action on excitatory and inhibitory **GABA**-mediated brain mechanisms. (3) Information on the neuropharmacol. action of the allylic acid stiripentol (STP) is limited. It increases brain **GABA** concns. by inhibition of its synaptosomal uptake or by decreasing its metabolic turnover, with a mechanism of action different from that of valproic acid. (4) Tiagabine (TGB), a nipecotic acid deriv., acts by inhibiting **GABA** re-uptake by glial cells and presynaptic neurons. (5) As zonisamide (ZNS) (1,2-benzioxazole-3-methanesulfonamide) has a sulfamoyl group in common with acetazolamide (AZA), it was suspected that its **anticonvulsant** activity could be related to a an inhibitory effect on carbonic anhydrase (CA). However, ZNS is 100 times less potent in vitro and 100-1000 times less potent ex vivo than AZA. Recent studies have demonstrated that the drug blocks voltage-sensitive sodium and calcium channels, so disrupting over-synchronized neuronal firing and subsequent epileptic activity.

L2 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:908479 CAPLUS
DOCUMENT NUMBER: 123:329900
TITLE: Effect of lamotrigine on the electrically evoked release of endogenous amino acids from slices of dorsal horn of the rat spinal cord
AUTHOR(S): Teoh, H.; Fowler, L. J.; Bowery, N. G.
CORPORATE SOURCE: Department Pharmacology, School Pharmacy, London, WC1N 1AX, UK
SOURCE: Neuropharmacology (1995), 34(10), 1273-8
CODEN: NEPHBW; ISSN: 0028-3908
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The novel antiepileptic lamotrigine has been shown to exhibit antinociceptive effects in the rat. In the present study, the effect of the drug on the elec. evoked release of endogenous amino acids from rat isolated spinal dorsal horn slices with intact dorsal roots was examd. and compared with that of morphine in the same prepn. Lamotrigine (0.1-300

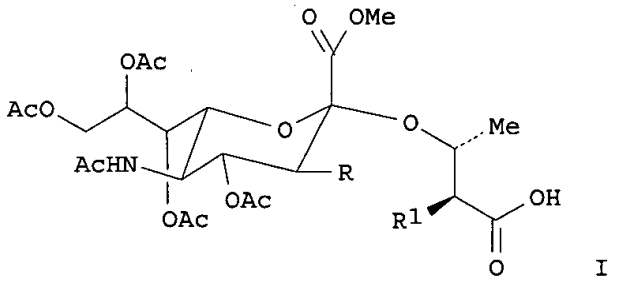
.mu.M) inhibited the release of aspartate, glutamate and **GABA** in a concn.-dependent manner. The lowest concns. of morphine tested (0.001-0.01 .mu.M) enhanced the stimulated release of aspartate and glutamate, while higher concns. inhibited their release. Elec. stimulated **GABA** release was reduced by lamotrigine in a concn.-dependent manner. Lamotrigine was more potent at inhibiting the release of glutamate (IC50 = 20 .mu.M) than that of **GABA** (IC50 = 44 .mu.M), supporting the previous suggestion that lamotrigine is a selective **inhibitor** of glutamate release. This suggests that the redn. in glutamate release could be one of the mechanisms by which lamotrigine exerts its antinociceptive effect.

LUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:165354 CAPLUS
DOCUMENT NUMBER: 102:165354
TITLE: Studies on the Maillard reaction. Part 13. Effect of the constitution of the **amino acid** on the course of the Maillard reaction
AUTHOR(S): Westphal, G.; Bochow, Christina; Kroh, L.
CORPORATE SOURCE: Sekt. Nahrungsgueterwirtsch. Lebensmitteltechnol., Humboldt-Univ. Berlin, Berlin, DDR-1040, Ger. Dem. Rep.
SOURCE: Nahrung (1985), 29(1), 69-74
CODEN: NAHRAR; ISSN: 0027-769X
DOCUMENT TYPE: Journal
LANGUAGE: German

AB Aq. solns. of D-glucose [50-99-7] were mixed with solns. of glycine [56-40-6], .alpha.-alanine [56-41-7], .beta.-alanine [107-95-9], .alpha.-aminobutyric acid [80-60-4], .gamma.-aminobutyric acid [56-12-2], leucine [61-90-5], lysine [56-87-1], .epsilon.-aminocaproic acid [60-32-2], or norleucine [327-57-1] and held at 100.degree.. Browning was measured spectrometrically. Every system except glucose-lysine had an induction period which in most cases lasted for 14-20 h. **Amino acids** with 2 or 6 C atoms between the CO2H and NH2 browned more rapidly with glucose than did the corresponding .alpha.- and .gamma.-aminobutyric acids, probably because of **lactam formation**.

L15 ANSWER 73 OF 96 CA

SOURCE: Perkin 1 (2000), (13), 2127-2133
CODEN: PERKF9
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 133:252698
GI



I

AB Three different sialic acid-contg. building blocks [(I); R = H, R1 = N3 (II); R = SPh, R1 = N3 (III); R = H, R1 = FmocNH- (IV)] were synthesized for use in solid-phase glycopeptide libraries. Investigation of the conditions for glycosylation of threonine (Thr) with various sialic acid donors revealed that the best results were obtained by coupling glycosyl xanthate 2 to the acceptors Fmoc-Thr-OH or the .alpha.-azido acid analog of Thr. Among several catalysts employed, phenylsulfanyl triflate (PST) afforded the best yields. Both the N-Fmoc and .alpha.-azido analogs of Thr allowed glycosylation with good stereoselectivity in 80% IV and 84% II yield, resp. Introduction of a phenylthio group in the 3 position of the sialic acid donor, to assist the stereoselective outcome of the glycosylation reaction, gave good results; however difficulties in the removal of the phenylthio auxiliary group made this route less attractive.

Both building blocks II and IV were successfully introduced in solid-phase glycopeptide synthesis. Interestingly, alk. deprotection of the Fmoc group of IV, necessary for subsequent introduction of **amino acids**, resulted in an immediate attack of the .alpha.-amino group on the sialic acid Me ester to form the lactam. This side reaction was also obsd. during redn. of the azido acid building block II under alk. conditions, but could be suppressed by performing the redn. under acidic conditions. **Lactam formation** was completely avoided by hydrolysis of the Me ester prior to redn. of the azide.

REFERENCE COUNT: 39
REFERENCE(S): (1) Alper, P; Tetrahedron Lett 1996, V37, P6029 CAPLUS
(2) Arsequell, G; Tetrahedron: Asymmetry 1997, V8, P2839 CAPLUS
(3) Cavender, C; J Org Chem 1972, V37, P3567 CAPLUS
(4) Christensen, M; J Chem Soc, Perkin Trans 1 1993, P1453 CAPLUS
(5) Christensen, M; J Chem Soc, Perkin Trans 1 1994, P1299 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

ACCESSION NUMBER: 2001084718 MEDLINE
DOCUMENT NUMBER: 20541411 PubMed ID: 11087406
TITLE: Structure and activities of constrained analogues of human parathyroid hormone and parathyroid hormone-related peptide: implications for receptor-activating conformations of the hormones.
AUTHOR: Barbier J R; MacLean S; Morley P; Whitfield J F; Willick G E
CORPORATE SOURCE: Institute for Biological Sciences, National Research Council, Ottawa, Ontario, Canada K1A 0R6.
SOURCE: BIOCHEMISTRY, (2000 Nov 28) 39 (47) 14522-30.
Journal code: A0G. ISSN: 0006-2960.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010118

AB Parathyroid hormone (PTH) has a helix-bend-helix structure in solution. Part of the C-terminal helix, residues 21-31, is amphiphilic and forms a critical receptor-binding region. Stabilization of this alpha-helix by **lactam formation** between residues spaced i, i + 4 on the polar face was previously reported to increase adenylyl cyclase-stimulating (AC) activity if between residues 22 and 26 but to diminish it if between residues 26 and 30 [Barbier et al. (1997) J. Med. Chem. 40, 1373-1380]. This work reports the effects of other cyclizations on the polar face, differing in ring size or position, on alpha-helix conformation, as measured by circular dichroism, and on AC-stimulating activity. All analogues cyclized between residues 22 and 26 had at least a 1. 5-fold increase in activity, suggesting an alpha-helical structure between about residues 21 and 26. Cyclization between residues 25 and 29 or residues 26 and 30 diminished activity by 20-30%, despite stabilizing alpha-helix, suggesting that residues 25-31 bind to the receptor in a helical, but not classical alpha-helical, conformation. Analogues cyclized between residues 13 and 17 had slightly increased activity. A bicyclic analogue, with lactams between residues 13 and 17 and residues 22 and 26, had about the same activity as that cyclized only between 22 and 26. Parathyroid hormone-related peptide (PTHrP) may bind in a manner similar to the common receptor, but hydrophobic moment calculations suggest that it must bind as a tighter helix in order to optimally present its hydrophobic residues to the receptor. Both PTHrP analogues cyclized between either residues 22 and 26 or residues 26 and 30 had more stable alpha-helices but reduced AC activities, consistent with this hypothesis.

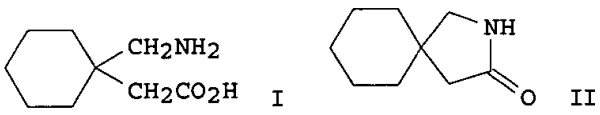
L15 ANSWER 6 OF 96 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 2
ACCESSION NUMBER: 2000:426639 CAPLUS
DOCUMENT NUMBER: 133:252698
TITLE: Synthesis and application of sialic acid-containing building blocks for glycopeptide libraries. Establishing glycosylation conditions
AUTHOR(S): Halkes, Koen M.; St. Hilaire, Phaedria M.; Jansson, Anita M.; Gotfredsen, Charlotte H.; Meldal, Morten
CORPORATE SOURCE: Department of Chemistry, Carlsberg Laboratory, Valby, Copenhagen, DK-2500, Den.

01 ISI (R)
ACCESSION NUMBER: 92:282498 SCISEARCH
THE GENUINE ARTICLE: HR116
TITLE: STABILITY STUDIES OF **GABAPENTIN** IN AQUEOUS-SOLUTIONS
AUTHOR: ZOUR E; LODHI S A; NESBITT R U; SILBERING S B; CHATURVEDI P R (Reprint)
CORPORATE SOURCE: WARNER LAMBERT PARKE DAVIS, PARKE DAVIS PHARMACEUT RES DIV, 170 TABOR RD, MORRIS PLAINS, NJ, 07950
COUNTRY OF AUTHOR: USA
SOURCE: PHARMACEUTICAL RESEARCH, (MAY 1992) Vol. 9, No. 5, pp. 595-600.
ISSN: 0724-8741.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 6

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Gabapentin** is a gamma-aminobutyric acid analogue, which has been shown to be an effective antiepileptic. The solution stability of **gabapentin** in buffered systems was studied in order to facilitate the formulation of a liquid product. The degradation of the drug was followed as a function of pH, buffer concentration, ionic strength, and temperature. The results indicated that the rate of degradation was proportional to the buffer concentration and temperature. The pH-rate profile of **gabapentin** degradation showed that the rate of degradation was minimum at an approximate pH of 6.0. Further, the data suggested a slower solvent-catalyzed degradation rate for the zwitterionic species compared to the cationic or anionic species in the pH range of 4.5 to 7.0. There was no influence of ionic strength on the rate of degradation. Arrhenius plots of the data indicated that a shelf life of 2 years or more at room temperature may be obtained in an aqueous solution at a pH value of 6.0.

L11 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 5
ACCESSION NUMBER: 1992:91232 CAPLUS
DOCUMENT NUMBER: 116:91232
TITLE: The effect of cyclodextrins on the rate of intramolecular lactamization of **gabapentin** in aqueous solution
AUTHOR(S): Kearney, A. S.; Mehta, S. C.; Radebaugh, G. W.
CORPORATE SOURCE: Parke-Davis Pharm. Res. Div., Warner-Lambert Co., Morris Plains, NJ, 07950, USA
SOURCE: Int. J. Pharm. (1992), 78(1), 25-34
CODEN: IJPHDE; ISSN: 0378-5173
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I II

AB The effect of various cyclodextrins on the intramol. lactamization of

gabapentin (I) in soln. was investigated. Baseline studies in the absence of cyclodextrins were conducted under accelerated conditions to obtain reaction rates that could be followed over a shorter time interval.

In aq. buffered solns. at 80.degree. and .mu. = 0.5 M, I undergoes an intramol. aminolysis to yield a stable, cyclized **lactam** product (II) over the pH range of 1.4-11.1. The buffer-independent pH-rate profile was described by two reaction pathways: a specific acid- and specific base-catalyzed lactamization of the uncharged species. Acetate and phosphate buffers were found to catalyze the rate of **lactam** formation, whereas borate had no apparent catalytic effect. Acetate appeared to be acting as a general-acid catalyst, whereas phosphate appeared to be acting as a general-acid and general-base catalyst. Next, the effect of various cyclodextrins on the lactamization rate was investigated over the pH range of 4.1-7.1. In the pH region defined as specific-acid catalyzed lactamization of the uncharged species, .alpha.- and .gamma.-cyclodextrin had minimal effect on the rate, whereas .beta.- and hydroxypropyl-.beta.-cyclodextrin accelerated the lactamization rate. While in the pH region defined as specific-base catalyzed lactamization of the uncharged species, all four cyclodextrins catalyzed the reaction rate (.beta.- > hydroxypropyl-.beta.- > .alpha.- .apprxeq. .gamma.-cyclodextrin). Interestingly, the catalytic efficiency of acetate buffer varied depending on the cyclodextrin involved. The catalytic efficiency was the greatest in the presence of .beta.-cyclodextrin which was followed by hydroxypropyl-.beta.-cyclodextrin. In 100 mM phosphate buffer of pH 7 and in the presence of varying concns. of the cyclodextrins, the rate of lactamization of I exhibited Michaelis-Menten-type kinetics. The data were consistent with relatively weak drug-cyclodextrin complex formation and with I being more chem. labile as complexed than uncomplexed drug. The enhanced rate obsd. in the presence of cyclodextrins was attributed to complexation-induced, conformational changes in the reactive moieties of I.

L11 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:450299 CAPLUS
DOCUMENT NUMBER: 115:50299
TITLE: Preparation of cyclic amino acid derivatives
INVENTOR(S): Steiner, Klaus; Herrmann, Wolfgang; Crone, Guenter; Combs, Charles Shepherd
PATENT ASSIGNEE(S): Goedecke A.-G., Fed. Rep. Ger.
SOURCE: Eur. Pat. Appl., 9 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

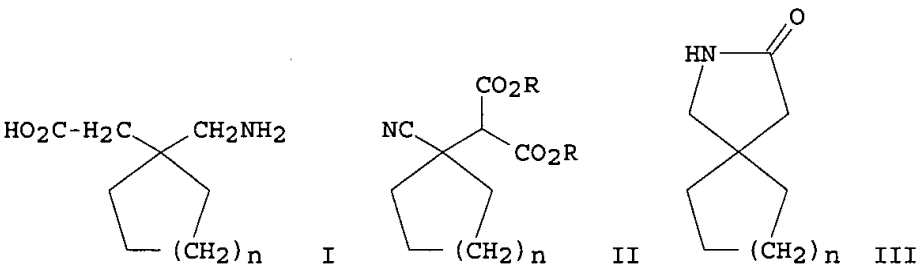
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 414275	A2	19910227	EP 1990-116293	19900824
EP 414275	A3	19910515		
EP 414275	B1	19931208		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
DE 3928184	A1	19910228	DE 1989-3928184	19890825
US 5068413	A	19911126	US 1990-570493	19900821
IL 95480	A1	19950629	IL 1990-95480	19900823
HU 54624	A2	19910328	HU 1990-5333	19900824

HU 208521	B	19931129			
JP 03090054	A2	19910416	JP 1990-221423	19900824	
JP 2839344	B2	19981216			
AT 98219	E	19931215	AT 1990-116293	19900824	
ES 2059938	T3	19941116	ES 1990-116293	19900824	

PRIORITY APPLN. INFO.: DE 1989-3928184 19890825
EP 1990-116293 19900824

OTHER SOURCE(S): MARPAT 115:50299

GI



AB The title compds. [I; n = 1-3 integer] are prepd. via alk. hydrolysis of (cyanocycloalkyl)malonates II [R = alkyl], decarboxylating the resulting II [R = H], catalytically hydrogenating the cyano group, and optionally hydrolyzing the byproducts, **lactams** III. II [R = Et, n = 2] was hydrolyzed with NaOH, the resulting II [R = H, n = 2] in toluene was heated 1 h at 80-85.degree., and the decarboxylated product hydrogenated over 5% Rh/C to give **gabapentin**.

DUPLICATE 4
ACCESSION NUMBER: 2001416398 MEDLINE
DOCUMENT NUMBER: 21357569 PubMed ID: 11465044
TITLE: The biotransformation of nitrogen containing xenobiotics to lactams.
AUTHOR: Vickers S; Polsky S L
CORPORATE SOURCE: Merck Research Laboratories, West Point, PA 19486, USA.. stanley_vickers@merck.com
SOURCE: Curr Drug Metab, (2000 Dec) 1 (4) 357-89. Ref: 138
Journal code: D3T; 100960533. ISSN: 1389-2000.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

AB The metabolism of nitrogen heterocyclics may lead to **lactam formation**. In early studies on xenobiotic metabolism lactams were identified as metabolites of nicotine, cyproheptadine, tremorine and prolintane. Now, because of the increasing availability of powerful analytical techniques, there are many instances of lactams being identified as metabolites. Lactam metabolites are formed from either iminium ions or carbinolamines. These two intermediates may have distinct mechanisms of formation but they can interconvert. There is evidence that the iminium ions are oxidized to lactams by aldehyde oxidases (cytosolic molybdenum hydroxylases). The tissue distribution and enzyme activities of aldehyde oxidase have been studied in several animal species. However, it is also known that iminium ions can undergo spontaneous hydrolysis to the corresponding carbinolamine. If the latter is stable it may undergo oxidation by cytochrome P-450 to form the lactam. Thus, species differences in **lactam formation** might be caused by differences in the concentrations of either cytochrome P450 isozymes or aldehyde oxidases. It appears that **lactam formation** is an end stage in the metabolism of N-heterocycles in that it is unlikely that the lactam will undergo hydrolysis to the corresponding **amino acid**. Such **amino acids** probably arise from the amino aldehydes that may be produced from ring opening of unstable carbinolamine intermediates. When microsomal preparations are incubated with the appropriate substrate in the presence of sodium cyanide the iminium ion may be trapped to produce a cyano compound. Such reactions have led to the proposal that iminium ions might react with nucleophilic sites of cellular macromolecules and so contribute to both the pharmacology and toxicology of N-heterocyclic compounds. Other pathways for the formation of lactam metabolites involve the internal cyclization of precursor metabolites, e.g. the self-condensation of an aldehyde group (formed during metabolism) with a neighboring amide group. However, spontaneous ring closures of **amino acids** to form lactams seem unlikely since it would be anticipated that the **amino acid** residue would exist as a stable zwitterion under physiological conditions. Thus, it is unlikely that lactams will undergo futile metabolism via hydrolytic ring opening followed by ring closure. Under extreme conditions such unanticipated ring closures may occur and the conditions of metabolite isolation may contribute to the occurrence of

0 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:429916 CAPLUS
DOCUMENT NUMBER: 115:29916
TITLE: Preparation of **lactam**-free 1-aminomethyl-1-carboxymethylcycloalkanes and drug compositions containing them
INVENTOR(S): Augart, Helmut; Gebhardt, Uwe; Herrmann, Wolfgang
PATENT ASSIGNEE(S): Goedecke A.-G., Fed. Rep. Ger.
SOURCE: Eur. Pat. Appl., 8 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 414263	A2	19910227	EP 1990-116265	19900824
EP 414263	A3	19910605		
EP 414263	B1	19941026		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
DE 3928183	A1	19910228	DE 1989-3928183	19890825
JP 03090053	A2	19910416	JP 1990-221422	19900824
JP 3148223	B2	20010319		
ES 2063219	T3	19950101	ES 1990-116265	19900824
JP 2001058976	A2	20010306	JP 2000-270023	19900824
US 6054482	A	20000425	US 1995-377618	19950125

PRIORITY APPLN. INFO.:
DE 1989-3928183 A 19890825
US 1990-570500 B1 19900821
JP 1990-221422 A3 19900824
US 1992-865723 B1 19920408
US 1993-20270 B1 19930218

OTHER SOURCE(S): MARPAT 115:29916
GI For diagram(s), see printed CA Issue.
AB Title compds. [I; n = 4-6] contg. <0.5 wt.% of the corresponding **lactams** (II) are prepd. by hydrolyzing II or crude I (obtained from II and still contg. II as an impurity) with concd. HCl until ring opening is complete, optionally followed by incorporating the **lactam**-free I into pharmaceutical compns. contg. excipients that do not catalyze formation of the **lactam**. **Gabapentin** **lactam** in H2O was refluxed with concd. HCl at 108.degree. for 6 h, the reaction mixt. cooled to 28.degree., the ppt. collected and dissolved in H2O and extd. with CH2Cl2 to give 60% I (n = 5).HCl.

DOCUMENT NUMBER: 132:6349
TITLE: Preparation of stabilized pharmaceuticals containing .gamma.-aminobutyric acid derivatives
INVENTOR(S): Aomatsu, Akira
PATENT ASSIGNEE(S): Warner-Lambert Company, USA
SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9959573	A1	19991125	WO 1999-US10190	19990510
W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9940735	A1	19991206	AU 1999-40735	19990510
BR 9910508	A	20010102	BR 1999-10508	19990510
EP 1077692	A1	20010228	EP 1999-924166	19990510
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NO 2000005768	A	20001114	NO 2000-5768	20001114

PRIORITY APPLN. INFO.: JP 1998-133113 A 19980515
WO 1999-US10190 W 19990510

OTHER SOURCE(S): MARPAT 132:6349

AB The present invention provides a stabilized pharmaceutical prepn. of a 4-amino-3-substituted butanoic acid deriv. which can be obtained by incorporating an amino acid as a stabilizer. Thus, a sample was prepd. by dissolving 500 mg of **gabapentin** crystals in water to make up a total vol. of 10 mL and stored under various conditions. The degrdn. of **gabapentin** stored, e.g., for 4 wk at 45.degree. was prevented by the addn. of L-**valine** or **glycine**.

REFERENCE COUNT: 4
REFERENCE(S):
(1) Ciba Geigy AG; EP 0376891 A 1990 CAPLUS
(2) Kigasawa, K; US 4952560 A 1990 CAPLUS
(3) Nitto Electric Ind Co Ltd; JP 63253022 A 1988 CAPLUS
(4) Warner Lambert Co; EP 0458751 A 1991 CAPLUS

L4 ANSWER 165 OF 169 MEDLINE DUPLICATE 29
ACCESSION NUMBER: 93205649 MEDLINE
DOCUMENT NUMBER: 93205649 PubMed ID: 8456077
TITLE: A saturable transport mechanism in the intestinal absorption of **gabapentin** is the underlying cause of the lack of proportionality between increasing dose and drug levels in plasma.
AUTHOR: Stewart B H; Kugler A R; Thompson P R; Bockbrader H N
CORPORATE SOURCE: Pharmacokinetics & Drug Metabolism Department, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, Michigan 48106-1047.
SOURCE: PHARMACEUTICAL RESEARCH, (1993 Feb) 10 (2) 276-81. Journal code: PHS; 8406521. ISSN: 0724-8741.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199304
ENTRY DATE: Entered STN: 19930507
Last Updated on STN: 19930507
Entered Medline: 19930422

AB **Gabapentin** (1-(aminomethyl)cyclohexaneacetic acid) is a neuroprotective agent with antiepileptic properties. The structure is small (molecular weight less than 200), is zwitterionic, and resembles an amino acid with the exception that it does not contain a chiral carbon and the amino group is not alpha to the carboxylate functionality. **Gabapentin** is not metabolized by humans, and thus, the amount of **gabapentin** excreted by the renal route represents the fraction of dose absorbed. Clinical trials have reported dose-dependent bioavailabilities ranging from 73.8 +/- 18.3 to 35.7 +/- 18.3% when the dose was increased from 100 to 1600 mg. The permeability of **gabapentin** in the rat intestinal perfusion system was consistent with carrier-mediated absorption, i.e., a 75 to 80% decrease in permeability when the drug concentration was increased from 0.01 to 50 mM (0.46 +/- 0.05 to 0.12 +/- 0.04). Excellent agreement was obtained between the actual clinical values and the predicted values from in situ results for the fraction of dose absorbed calculated using the theoretically derived correlation, Fabs = 1 - exp(-2Peff) by Amidon et al. (Pharm. Res. 5:651-654, 1988). The permeability values obtained for **gabapentin** correspond to 67.4 and 30.2% of the dose absorbed at the low and high concentrations, respectively. In the everted rat intestinal ring system, **gabapentin** shared an inhibition profile similar to that of L-**phenylalanine**. Characteristics of **gabapentin** uptake included cross-inhibition with L-Phe, sensitivity to inhibition by L-Leu, stereoselectivity as evidenced by incomplete inhibition by D-Phe, and lack of effect by Gly. (ABSTRACT TRUNCATED AT 250 WORDS)

DUPLICATE 26
ACCESSION NUMBER: 94139837 MEDLINE
DOCUMENT NUMBER: 94139837 PubMed ID: 8307106
TITLE: 3H]**gabapentin** may label a system-L-like neutral amino acid carrier in brain.
AUTHOR: Thurlow R J; Brown J P; Gee N S; Hill D R; Woodruff G N
CORPORATE SOURCE: Parke-Davis Neuroscience Research Centre, Addenbrookes Hospital Site, Cambridge, UK.
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1993 Nov 15) 247 (3) 341-5.
Journal code: EN6; 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199403
ENTRY DATE: Entered STN: 19940330
Last Updated on STN: 19940330
Entered Medline: 19940311

AB The ability of large neutral amino acids to interact with a site in mouse and pig brain labelled by [3H]**gabapentin** was examined. As previously described for rat tissue, [3H]**gabapentin** bound to synaptic plasma membranes prepared from mouse or pig cerebral cortex with high affinity (Kinetically derived KD = 14 and 17 nM for mouse and pig, respectively). Equilibrium binding in each species was inhibited by **gabapentin** and a range of large neutral amino acids. L-leucine (IC50 = 80 nM), L-**isoleucine** (IC50 = 72 nM), L-norleucine (IC50 = 40 nM) and L-methionine (IC50 = 50 nM) were the most potent of those tested. Binding was also inhibited by L-**phenylalanine** (IC50 = 380 nM), L-**valine** (IC50 = 310 nM) and the selective system-L substrate 2-amino-2-carboxy-bicycloheptane (IC50 = 420 nM) but not by the sodium-dependent System-A substrate methylaminoisobutyric acid. The presence of a submaximal concentration of leucine reduced [3H] **gabapentin** binding affinity but did not affect the maximum number of binding sites, suggesting a competitive interaction between leucine and the binding protein. The results suggest [3H]**gabapentin** may label a site in brain that resembles the large neutral amino acid transporter described in other tissues.

L4 ANSWER 161 OF 169 BIOSIS COPYRIGHT 2001 BIOSIS

L4 ANSWER 144 OF 169 MEDLINE DUPLICATE 21
ACCESSION NUMBER: 96261486 MEDLINE
DOCUMENT NUMBER: 96261486 PubMed ID: 8925804
TITLE: Effect of a high-protein meal on **gabapentin** pharmacokinetics.
AUTHOR: Gidal B E; Maly M M; Budde J; Lensmeyer G L; Pitterle M E; Jones J C
CORPORATE SOURCE: University of Wisconsin, School of Pharmacy, Madison 53706, USA.
SOURCE: EPILEPSY RESEARCH, (1996 Feb) 23 (1) 71-6.
Journal code: EMA; 8703089. ISSN: 0920-1211.
PUB. COUNTRY: Netherlands
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19990129
Entered Medline: 19961118

AB The anticonvulsant **gabapentin** is transported across biological membranes via the L-amino acid transport system (System-L). Absorption of **gabapentin** is saturable, and in-vitro data have previously demonstrated that both L-leucine and L-**phenylalanine** may compete with the intestinal transport of **gabapentin**. The purpose of this study therefore was to determine whether a high-protein meal would interfere with **gabapentin** absorption. Ten healthy volunteers received in a randomized, cross-over design, a single 600-mg dose of **gabapentin** in the fasting state and after a high-protein meal consisting of 80 gm total protein (4.1 g **phenylalanine**, 8.2 g leucine and 4.2 g **isoleucine**), 52 g carbohydrate, and 9 g fat. Plasma **gabapentin** concentrations were measured by HPLC at baseline, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, 30 h. Calculated pharmacokinetic parameters included Cmax' Tmax' AUC and T1/2. In addition, a pharmacodynamic assessment (using visual analog scales) of **gabapentin**-related adverse effects was performed at 2 h post drug ingestion and was compared between study phases. Statistical analysis included Student's t-test for paired data, with significance assigned at $P < 0.05$. Cmax was significantly increased by 36% (3.87 +/- 1.15 vs 5.28 +/- .97 micrograms/ml, $P = 0.002$), and Tmax tended to be shorter (3.9 +/- 1.8 vs 2.8 +/- .35 h, $P = 0.10$), after the high-protein meal. Although AUC was increased by 11%, this did not achieve statistical significance. Despite significantly higher plasma concentrations at 2 h, subjects reported significantly fewer adverse effects after the high-protein meal. Potential mechanisms to explain these unexpected findings may be that the large amino acid load delivered with the high-protein meal enhanced **gabapentin** absorption via trans-stimulation, the process by which acutely increased intestinal luminal amino acid concentrations result in an acute up regulation in System-L activity. Conversely, the decrease in perceived adverse CNS effects of **gabapentin** following the high-protein meal may reflect CNS competition for System-L transport.

L4 ANSWER 145 OF 169 MEDLINE DUPLICATE 22
ACCESSION NUMBER: 97035281 MEDLINE
DOCUMENT NUMBER: 97035281 PubMed ID: 8880937
TITLE: The antiepileptic agent **gabapentin** (Neurontin)

possesses anxiolytic-like and antinociceptive actions that are reversed by D-**serine**.

AUTHOR: Singh L; Field M J; Ferris P; Hunter J C; Oles R J; Williams R G; Woodruff G N
CORPORATE SOURCE: Department of Biology, Parke-Davis Neuroscience Research Center, Cambridge, UK.
SOURCE: PSYCHOPHARMACOLOGY, (1996 Sep) 127 (1) 1-9.
Journal code: QGI; 7608025. ISSN: 0033-3158.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19970110

AB This report describes the activity of the antiepileptic agent **gabapentin** (Neurontin) in animal models predictive of anxiolysis and analgesia. **Gabapentin** displayed anxiolytic-like action in the rat conflict test, the mouse light/dark box and the rat elevated X-maze with respective minimum effective doses (MEDs) of 3, 10 and 30 mg/kg. Furthermore, **gabapentin** also induced behavioural changes suggestive of anxiolysis in the marmoset human threat test with a MED of 30 mg/kg. In the rat formalin test of tonic nociception, **gabapentin** dose-dependently (30-300 mg/kg) and selectively blocked the late phase with a MED of 100 mg/kg. However, it failed to block carrageenan-induced paw oedema. The intracerebroventricular (ICV) administration of the **glycine**/NMDA receptor agonist D-**Serine**, dose-dependently (10-100 micrograms/animal) reversed the antinociceptive action of **gabapentin** (200 mg/kg, SC). D-**Serine** (30 micrograms/animal, ICV) also reversed the anxiolytic-like effects (in the light/dark box and the rat elevated X-maze) of **gabapentin** (30 mg/kg). In contrast, L-**Serine** (100 micrograms, ICV) failed to block the antinociceptive action of **gabapentin**. The antinociceptive action of (+)-HA-966 (25 mg/kg, SC), a partial agonist at the **glycine**/NMDA receptor, was reversed by D-**Serine** (100 micrograms/animal, ICV). However, D-**Serine** (100 micrograms/animal, ICV) failed to affect the antinociceptive action of a competitive NMDA receptor antagonist CGS 19755 (3 mg/kg, SC). **Gabapentin** has negligible affinity for the strychnine insensitive [3H]**glycine** binding site. This indicates that the interaction between **gabapentin** and D-**Serine** may not involve the NMDA receptor complex. **Gabapentin** may represent a novel type of anxiolytic and analgesic agent.

L4 ANSWER 142 OF 169 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:100537 CAPLUS
DOCUMENT NUMBER: 126:139367
TITLE: Mechanisms of action of **gabapentin**
AUTHOR(S): Brown, J. P.; Boden, P.; Singh, L.; Gee, N. S.
CORPORATE SOURCE: Parke-Davis Neuroscience Research Centre, Cambridge University, Cambridge, CB2 2QB, UK
SOURCE: Rev. Contemp. Pharmacother. (1996), 7(5), 203-214
CODEN: RCPHFW; ISSN: 0954-8602
PUBLISHER: Marius Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with over 80 refs. **Gabapentin** [1-(aminomethyl)-cyclohexaneacetic acid; Neurontin.RTM.] is an antiepileptic drug that is structurally related to .gamma.-amino-butyric acid (GABA). It has a unique spectrum of activity in animal seizure models and has demonstrable efficacy in patients with refractory epilepsy. Although designed as a GABA-mimetic, **gabapentin** does not interact with any of the known pharmacol. sites on either the GABAA or GABAB receptor, nor does it block GABA uptake or inhibit the GABA-metabolizing enzyme, GABA transaminase. **Gabapentin** has been shown to elevate GABA levels in various brain regions of the rat but the relevance of this effect to the anticonvulsant activity of the drug remains unclear. Some electrophysiol. studies suggest that **gabapentin** may act as a partial agonist at the **glycine** modulatory site of the NMDA receptor. The reversal of the anticonvulsant effects of **gabapentin** in animal seizure models by D-**serine**, an agonist at the **glycine** modulatory site, further supports this notion. However, radioligand binding studies provide no evidence for any direct interaction of **gabapentin** with the NMDA receptor. A novel high affinity binding site for [3H] **gabapentin** has been identified in rat, mouse and pig brain membranes. While none of the front-line antiepileptic drugs has a high affinity for this site, several 3-substituted analogs of GABA and neutral amino acids, such as L-leucine, potently inhibit [3H]**gabapentin** binding. The binding protein has recently been purified to homogeneity and identified as the .alpha.2.delta. subunit of a voltage-dependent calcium channel (VDCC). Finally, behavioral studies suggest that **gabapentin** possesses not only antiepileptic but also anxiolytic and antinociceptive/anti-hyperalgesic properties. Further expts. are required to det. which, if any, of these behavioral effects are related to the interaction of **gabapentin** with GABAergic systems, NMDA receptors or neuronal VDCCs.

L4 ANSWER 143 OF 169 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96126571 EMBASE
DOCUMENT NUMBER: 1996126571
TITLE: [Sleep disorders in neurological diseases]. SCHLAFSTORUNGEN BEI NEUROLOGISCHEN ERKRANKUNGEN.
AUTHOR: Schilling F.
CORPORATE SOURCE: Klinikum, Klinik und Poliklinik f. Neurologie, PSF 595,99012 Erfurt, Germany
SOURCE: Zeitschrift fur Arztliche Fortbildung, (1996) 90/2 (131-137).
ISSN: 0044-2178 CODEN: ZAFBAX
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
020 Gerontology and Geriatrics

032 Psychiatry
037 Drug Literature Index
LANGUAGE: German
SUMMARY LANGUAGE: German; English
AB Sleep disorders in central or peripheral nervous system diseases frequently occur, but they often are neglected in diagnosis and therapy. During the last 20 years, sleep medicine has obtained more and more importance. It is possible to draw conclusions about the topical organization of sleep-wake-regulation by investigating of certain diseases. In the following survey the most important clinical pictures in neurology are described in consideration of an affected sleep. Typical symptoms and polysomnographic findings as well as recommendations for therapy are demonstrated.

L4 ANSWER 144 OF 169 MEDLINE DUPLICATE 21
ACCESSION NUMBER: 96261486 MEDLINE
DOCUMENT NUMBER: 96261486 PubMed ID: 8925804
TITLE: Effect of a high-protein meal on **gabapentin** pharmacokinetics.
AUTHOR: Gidal B E; Maly M M; Budde J; Lensmeyer G L; Pitterle M E; Jones J C
CORPORATE SOURCE: University of Wisconsin, School of Pharmacy, Madison 53706, USA.
SOURCE: EPILEPSY RESEARCH, (1996 Feb) 23 (1) 71-6.
Journal code: EMA; 8703089. ISSN: 0920-1211.
PUB. COUNTRY: Netherlands
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19990129
Entered Medline: 19961118
AB The anticonvulsant **gabapentin** is transported across biological membranes via the L-amino acid transport system (System-L). Absorption of **gabapentin** is saturable, and in-vitro data have previously demonstrated that both L-leucine and L-**phenylalanine** may compete with the intestinal transport of **gabapentin**. The purpose of this study therefore was to determine whether a high-protein meal would interfere with **gabapentin** absorption. Ten healthy volunteers received in a randomized, cross-over design, a single 600-mg dose of **gabapentin** in the fasting state and after a high-protein meal consisting of 80 gm total protein (4.1 g **phenylalanine**, 8.2 g leucine and 4.2 g **isoleucine**), 52 g carbohydrate, and 9 g fat. Plasma **gabapentin** concentrations were measured by HPLC at baseline, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, 30 h. Calculated pharmacokinetic parameters included Cmax' Tmax' AUC and T1/2. In addition, a pharmacodynamic assessment (using visual analog scales) of **gabapentin**-related adverse effects was performed at 2 h post drug ingestion and was compared between study phases. Statistical analysis included Student's t-test for paired data, with significance assigned at $P < 0.05$. Cmax was significantly increased by 36% (3.87 +/- 1.15 vs 5.28 +/- .97 micrograms/ml, $P = 0.002$), and Tmax tended to be shorter (3.9 +/- 1.8 vs 2.8 +/- .35 h, $P = 0.10$), after the high-protein meal. Although AUC was increased by 11%, this did not achieve statistical significance. Despite significantly higher plasma concentrations at 2 h, subjects reported significantly fewer adverse effects after the

high-protein meal. Potential mechanisms to explain these unexpected findings may be that the large amino acid load delivered with the high-protein meal enhanced **gabapentin** absorption via trans-stimulation, the process by which acutely increased intestinal luminal amino acid concentrations result in an acute up regulation in System-L activity. Conversely, the decrease in perceived adverse CNS effects of **gabapentin** following the high-protein meal may reflect CNS competition for System-L transport.

L4 ANSWER 139 OF 169 MEDLINE DUPLICATE 19
ACCESSION NUMBER: 96358001 MEDLINE
DOCUMENT NUMBER: 96358001 PubMed ID: 8762065
TITLE: Comparison of the autoradiographic binding distribution of [3H]-**gabapentin** with excitatory amino acid receptor and amino acid uptake site distributions in rat brain.
AUTHOR: Thurlow R J; Hill D R; Woodruff G N
CORPORATE SOURCE: Parke-Davis Neuroscience Research Centre, Addenbrookes Hospital Site, Cambridge.
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (1996 Jun) 118 (3) 457-65.
Journal code: B00; 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970305
Last Updated on STN: 19970305
Entered Medline: 19970214

AB 1. **Gabapentin** is a novel anticonvulsant with an unknown mechanism of action. Recent homogenate binding studies with [3H]-**gabapentin** have suggested a structure-activity relationship similar to that shown for the amino acid transport system responsible for the uptake of large neutral amino acids (LNAA). 2. The autoradiographic binding distribution of [3H]-**gabapentin** in rat brain was compared with the distributions for excitatory amino acid receptor subtypes and the uptake sites for excitatory and large neutral amino acids in consecutive rat brain sections. 3. Densitometric measurement of the autoradiographic images followed by normalisation with respect to the hippocampus CA1 stratum radiatum, was carried out before comparison of each binding distribution with that of [3H]-**gabapentin** by linear regression analysis. The correlation coefficients observed showed no absolute correlation was observed between the binding distributions of [3H]-**gabapentin** and those of the excitatory amino acid receptor subtypes. The acidic and large neutral amino acid uptake site distributions demonstrated a much closer correlation to the [3H]-**gabapentin** binding site distribution. The correlation coefficients for D-[3H]-aspartate, L-[3H]-leucine and L-[3H]-**isoleucine** binding site distributions were 0.76, 0.90 and 0.88 respectively. 4. Concentration-dependent inhibition by unlabelled **gabapentin** of autoradiographic binding of L-[3H]-leucine and L-[3H]-**isoleucine** was observed, with non-specific binding levels being reached at concentrations between 10 and 100 microM. 5. Excitotoxic quinolinic acid lesion studies in rat brain caudate putamen and autoradiography were carried out for the amino acid uptake sites mentioned above. The resulting glial infiltration of the lesioned areas was visualized by autoradiography using the peripheral benzodiazepine receptor specific ligand [3H]-PK11195. A significant decrease in binding density in the lesioned area compared with sham-operated animals was observed for D-[3H]-aspartate, L-[3H]-leucine, L-[3H]-**isoleucine** and [3H]-**gabapentin**, whilst [3H]-PK11195 showed a significant increase in binding density indicative of glial infiltration into the lesioned area. These results

suggest that the **gabapentin** binding site and the acidic and LNAA uptake site may be present on cell bodies of a neuronal population of cells. 6. From these studies it appears that [3H]-**gabapentin**, L-[3H]-leucine and L-[3H]-**isoleucine** bind to the same site in rat brain. The inhibition of [3H]-**gabapentin** binding by the LNAA uptake system-specific ligand, BCH, suggests that [3H]-**gabapentin** may label this uptake site, termed system-L. Conversely these ligands could be labelling a novel site that coincidentally has a similar structure-activity relationship to this uptake site. These results suggest a novel mechanistically relevant site of action for **gabapentin** and may enable further anti-epileptic agents of this type to be developed.

L4 ANSWER 119 OF 169 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 97413459 MEDLINE
DOCUMENT NUMBER: 97413459 PubMed ID: 9269874
TITLE: Contrasting nutrient effects on the plasma levels of an amino acid-like antiepileptic agent from jejunal administration in dogs.
AUTHOR: Stevenson C M; Radulovic L L; Bockbrader H N; Fleisher D
CORPORATE SOURCE: Pharmaceutical Research & Development, Whitehall-Robins Health Care, Hammonton, NJ 08037, USA.
SOURCE: JOURNAL OF PHARMACEUTICAL SCIENCES, (1997 Aug) 86 (8) 953-7.
Journal code: JO7; 2985195R. ISSN: 0022-3549.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19971008
Last Updated on STN: 19971008
Entered Medline: 19970925

AB The absorption of **gabapentin** was investigated by monitoring drug plasma levels as a function of time following midjejunal administration in mongrel dogs. From previous work, dose-dependent absorption had been postulated to be a consequence of carrier-mediated transport and a paracellular pathway had been postulated to contribute to the passive absorption component in mammalian small intestine. The potential for amino acid inhibition of the carrier-mediated absorption component was investigated by drug coinfusion with leucine and **phenylalanine**. The potential for monosaccharide-enhanced increases in drug absorption was studied by drug coinfusion with D-glucose and 3-O-methylglucose. While lower drug plasma levels were observed with amino acid coinfusion versus controls in each of the dogs studied, mean area under the plasma level time curves (AUC) were not statistically significantly different ($p \leq 0.07$). Monosaccharide coinfusion significantly increased **gabapentin** AUC over control studies ($p \leq 0.014$) and over coinfusion with L-system amino acids ($p \leq 0.0025$). Implications for the mechanisms of intestinal absorption of this amino acid-like antiepileptic drug in this canine model are discussed.

L4 ANSWER 111 OF 169 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 1998211510 MEDLINE
DOCUMENT NUMBER: 98211510 PubMed ID: 9551785
TITLE: A summary of mechanistic hypotheses of **gabapentin** pharmacology.
AUTHOR: Taylor C P; Gee N S; Su T Z; Kocsis J D; Welty D F; Brown J
P; Dooley D J; Boden P; Singh L
CORPORATE SOURCE: Department of Neuroscience Therapeutics, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Co., Ann Arbor, MI 48105, USA.
SOURCE: EPILEPSY RESEARCH, (1998 Feb) 29 (3) 233-49. Ref: 114
Journal code: EMA; 8703089. ISSN: 0920-1211.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980611
Last Updated on STN: 19980611
Entered Medline: 19980529

AB Although the cellular mechanisms of pharmacological actions of **gabapentin** (Neurontin) remain incompletely described, several hypotheses have been proposed. It is possible that different mechanisms account for anticonvulsant, antinociceptive, anxiolytic and neuroprotective activity in animal models. **Gabapentin** is an amino acid, with a mechanism that differs from those of other anticonvulsant drugs such as phenytoin, carbamazepine or valproate. Radiotracer studies with [14C]**gabapentin** suggest that **gabapentin** is rapidly accessible to brain cell cytosol. Several hypotheses of cellular mechanisms have been proposed to explain the pharmacology of **gabapentin**: 1. **Gabapentin** crosses several membrane barriers in the body via a specific amino acid transporter (system L) and competes with leucine, **isoleucine**, **valine** and **phenylalanine** for transport. 2. **Gabapentin** increases the concentration and probably the rate of synthesis of GABA in brain, which may enhance non-vesicular GABA release during seizures. 3. **Gabapentin** binds with high affinity to a novel binding site in brain tissues that is associated with an auxiliary subunit of voltage-sensitive Ca2+ channels. Recent electrophysiology results suggest that **gabapentin** may modulate certain types of Ca2+ current. 4. **Gabapentin** reduces the release of several monoamine neurotransmitters. 5. Electrophysiology suggests that **gabapentin** inhibits voltage-activated Na+ channels, but other results contradict these findings. 6. **Gabapentin** increases serotonin concentrations in human whole blood, which may be relevant to neurobehavioral actions. 7. **Gabapentin** prevents neuronal death in several models including those designed to mimic amyotrophic lateral sclerosis (ALS). This may occur by inhibition of glutamate synthesis by branched-chain amino acid aminotransferase (BCAA-t).

ANSWER 1 OF 1 CAPLUS COPYRIGHT 2001 ACS
AN **1992:433682** CAPLUS
DN 117:33682
TI Coated delivery system for cyclic amino acids with improved taste, texture
and compressibility
IN Cherukuri, Subraman Rao; Chau, Tommy Linkwong
PA Warner-Lambert Co., USA
SO Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 458751	A1	19911127	EP 1991-810380	19910517
R: BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE				
JP 04270216	A2	19920925	JP 1991-148198	19910524
PRAI US 1990-530768		19900525		

OS MARPAT 117:33682
AB A core made of a cyclic amino acid (Markush given), such as the drug Gabapentin is first coated with a water-sol. or water-insol. polymeric film and then with a hydrophilic coating made of fats, fatty acids and/or waves. Unmilled Gabapentin was granulated with excipients and coated with gelatin type A and then with a mixt. of partially-hydrogenated soybean oil and glycerol monostearate.

AN **1989:101861** CAPLUS
DN 110:101861
TI Transdermal preparations containing baclofen
IN Watanabe, Shigeyuki; Sato, Susumu
PA Nitto Denko Corp., Japan
SO Jpn. Kokai Tokkyo Koho, 4 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 63253022	A2	19881020	JP 1987-86354	19870408

AB Transdermal prepns. contain baclofen. A prepn. (comprising propylene glycol 0.50, octyl alc. 0.10, citrate buffer 0.40 mL, and 10 mg baclofen) was applied at 0.1 mL to an isolated rat skin, resulting in 540 .mu.g baclofen permeation, vs. 30 .mu.g, in the absence of octyl alc.

L8 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2001 ACS
AN **1986:39763** CAPLUS
DN 104:39763
TI Ointment base
IN Kigasawa, Kazuo; Ohtani, Hideaki; Tanaka, Makoto; Hayashida, Shigeru
PA Takeda Chemical Industries, Ltd. , Japan
SO Eur. Pat. Appl., 41 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 159167	A2	19851023	EP 1985-302402	19850404
	EP 159167	A3	19860115		
	EP 159167	B1	19910717		
	R: BE, CH, DE, FR, GB, IT, LI, NL, SE				
	JP 60214730	A2	19851028	JP 1984-66711	19840405
	JP 61186311	A2	19860820	JP 1985-24394	19850213
	CA 1249968	A1	19890214	CA 1985-478002	19850401
	US 4952560	A	19900828	US 1988-183307	19880411
PRAI	JP 1984-66711		19840405		
	JP 1985-24394		19850213		
	US 1985-720402		19850405		

AB Ointments contg. a water-sol. protein, a monohydric alc., and/or an oleaginous substance, as well as a wetting agent, are highly effective vehicles for the cutaneous absorption of drugs. Thus, an ointment was prepd., contg. indomethacin 1.0, gelatin 3.0, hydroxyethyl cellulose 1.7, glycerol 4.0, EtOH 35, and water 55.3 g. Indomethacin showed faster release from this ointment than from a com. prepn., when tested on a Millipore SSWP 047 membrane adjoining a phosphate buffer (pH 5.5).

N **1991:129099** CAPLUS
DN 114:129099
TI Buccal tablets containing baclofen
IN Khanna, Satish Chandra
PA Ciba-Geigy A.-G., Switz.
SO Eur. Pat. Appl., 8 pp.
CODEN: EPXXDW
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 376891	A1	19900704	EP 1989-810981	19891222
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	AU 8947177	A1	19900705	AU 1989-47177	19891221
	AU 628455	B2	19920917		
	CA 2006771	AA	19900630	CA 1989-2006771	19891228
	ZA 8909947	A	19900829	ZA 1989-9947	19891228
	JP 02221219	A2	19900904	JP 1989-338861	19891228
	DK 8906734	A	19900701	DK 1989-6734	19891229
	US 5091184	A	19920225	US 1991-693769	19910426
PRAI	CH 1988-4855		19881230		
	US 1989-450645		19891214		

AB The title tablets which are adhesive to the mouth mucosa, comprise a hydrophilic core contg. baclofen, a swellable vinyl polymer, a galactomannan and/or a wax and/or a hydrogenated glyceride. The core is partially covered with a hydrophilic coating. Granules were made, contg. baclofen 25.00, Meyproqat-150 (galactomannan) 42.16, Carbopol-934P (acrylic polymer) 22.39, Mg stearate 0.45 mg, and 15 mL water. The granules were shaped into tablets and coated on 1 side with a mixt. of polyethylene glycol 44, sucrose 29, water 52 and EtOH 22 g. The tablets are spasmolytic.

CCESSION NUMBER: 1990:70029 CAPLUS
DOCUMENT NUMBER: 112:70029
TITLE: **Phenylglycines** for use in reducing neurotoxic injury
INVENTOR(S): Cordi, Alex A.; Vazquez, Michael L.
PATENT ASSIGNEE(S): Searle, G. D., and Co., USA
SOURCE: Eur. Pat. Appl., 28 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 313002	A2	19890426	EP 1988-117358	19881019
EP 313002	A3	19900711		
EP 313002	B1	19931201		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
US 4918064	A	19900417	US 1987-111749	19871021
AT 97904	E	19931215	AT 1988-117358	19881019
ES 2060635	T3	19941201	ES 1988-117358	19881019
JP 01135790	A2	19890529	JP 1988-265218	19881020

PRIORITY APPLN. INFO.: US 1987-111749 19871021
EP 1988-117358 19881019
OTHER SOURCE(S): CASREACT 112:70029; MARPAT 112:70029
GI For diagram(s), see printed CA Issue.
AB **Phenylglycine** derivs. I [R1-R4 = H, alkyl, cycloalkyl, aralkyl, aryl, haloalkyl, halo, cyano, NO2, OR5, SR5, C(O)R5, C(S)R5, CO2R5, O2CR5, (substituted) amino, (substituted) amido; R5 = H, alkyl, aryl, aralkyl; R6 = H, alkyl, acyl, aryl, aralkyl, CO2R5; Z = OR5, SR5, (substituted) amino, OCHR7O2CR5; R7 = H, alkyl] and their salts are prepd. for use in reducing neurotoxic injury from excitatory amino acids assocd. with anoxia or ischemia after stroke, cardiac arrest, or perinatal asphyxia. Thus, 4-(diethylphosphonomethyl)benzaldehyde was converted to .alpha.-amino-4-(diethylphosphonomethyl)phenylacetonitrile and hydrolyzed with HCl to 4-(phosphonomethyl)**phenylglycine** (II). II (50 .mu.M) protected cultured hippocampal neurons from cell death du

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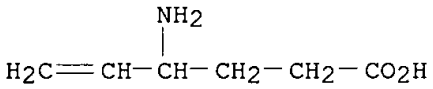
CN 5-Hexenoic acid, 4-amino-, (.+-.)-
OTHER NAMES:
CN (.+-.)-.gamma.-Vinyl GABA
CN (.+-.)-4-Amino-5-hexenoic acid
CN .gamma.-Vinyl-.gamma.-aminobutyric acid
CN .gamma.-Vinyl-GABA
CN 4-Amino-5-hexenoic acid
CN GVG
CN MDL 71754
CN RMI 71754
CN Sabril
CN **Vigabatrin**
FS 3D CONCORD
DR 60643-86-9
MF C6 H11 N O2
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, PHAR, PHARMASEARCH, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



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CN (S)-4-Amino-5-hexenoic acid
CN **(S)-Vigabatrin**
CN 4(S)-Amino-5-hexenoic acid
CN RMI 71890
CN **S-(+)-Vigabatrin**
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MF C6 H11 N O2
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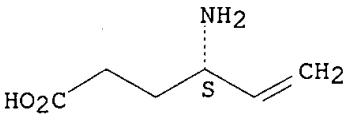

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CN PD 144723
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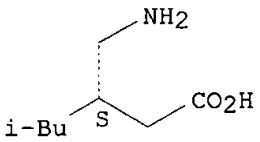

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L1 ANSWER 18 OF 18 REGISTRY COPYRIGHT 2003 ACS
RN 2763-96-4 REGISTRY
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OTHER CA INDEX NAMES:
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OTHER NAMES:
CN 3-Hydroxy-5-aminomethylisoxazole
CN 5-(Aminomethyl)-3-isoxazolol
CN Agarin
CN Agarine
CN **Muscimol**
CN Pantherine
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CI COM
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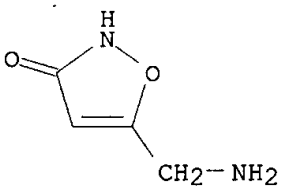

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5 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

MEDI

Recent Developments In The Treatment of Childhood Epilepsy

New Drugs For Epilepsy
Applications in Pediatric Practice

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Learning Objectives:

1. Specify the major types of epilepsy and the indications for various new antiepileptic drugs (AEDs).
2. Understand the uses and limitations of clinical AED studies carried out prior to marketing.
3. Describe the essential pharmacokinetics and pharmacodynamics of fosphenytoin, lamotrigine, gabapentin, topiramate, and tragaline.
4. Understand strategies for improving compliance, minimizing drug toxicity, managing refractory seizures.

New Drugs For Epilepsy Applications in Pediatric Practice

Development of effective new drugs for epilepsy did not occur as rapidly as pharmacological advances for other diseases. Four commercially available drugs were commonly used in the United States in the early 1990's: phenobarbital phenytoin, carbamazepine, and valproate (or the related compound, divalproex sodium). These drugs were introduced in 1912, 1938, 1974, and 1978, respectively. Less commonly although still widely used were primidone, ethosuximide and clonazepam, which were marketed in 1954, 1960, and 1975. The eight remaining antipeptic drugs (AEDS) marketed in the United States prior to 1993 were rarely prescribed. Since 1994, six new AEDs have become available: felbamate, lamotrigine, gabapentin, topiramate, and tiagabine. An intravenous form of valproate has also been marketed. Other drugs which are likely to be released in the near future include oxcarbazepine,

vigabatrin, and clobazam.

Merritt and Putnam ushered in the modem era of systematic testing of potential AEDs by the introduction of phenytoin, which was found to be and effective agent when multiple drugs were screened against an animal model of epilepsy. Since 1945, expanded laboratory models of epilepsy have allowed more systematic screening and testing of potential antiseizure agents. On the other hand, FDA regulations requiring demonstration of efficacy as well as safety prior to approval have slowed marketing of new medications although undoubtedly providing some assurance that they will have a favorable risk: benefit profile.

The incidence curve for epilepsy has two peaks, one in childhood and another in old age. Epilepsy develops in approximately 30,000 children and adolescents in the United States each year. This figure does not include the 100,000 children who experience a febrile seizure or the 20,000 who have either a single unprovoked seizure; a seizure due to various, transient, CNS insults; or neonatal seizures. (Discuss prevalence data here)

Adequate seizure control cannot be achieved in 15 to 30% of epileptic patients with currently available drug therapy. Unfortunately, not all patients with medically intractable seizures are suitable candidates for epilepsy surgery and many suitable candidates are probably not referred for surgery. If all patients with uncontrolled seizures could receive the benefit of surgery without regard to economic or geographic considerations, many more epilepsy surgery centers would be necessary to handle he increased volume. Development of new, highly effective drugs rather than epilepsy surgery appears to be the major source of hope for the majority of patients with intractable epilepsy.

This brief review discusses recently released antiepileptic drugs as well as a few antiepileptic drugs which may be marketed in the near future.

Felbamate

Felbamate, a derivative of the antianxiety drug meprobamate, was released in the United States in 1994 and was considered to be a very promising agent because of its broad spectrum of efficacy and apparently low toxicity. After 8 months, it became evident that an unacceptably high incidence of aplastic anemia and hepatopathy were associated with this drug, Prior to release, experience with the drug consisted of approximately 5000 patient years. The high incidence of aplastic anemia (one case per 5000 patient years) only became evident after an experience of approximately 50,000 patient years. This observation demonstrates that premarketing studies may fail to detect relatively rare but extremely serious adverse drug effects and suggests that pediatricians and pediatric neurologists should not use most newly released agents as first line therapy. After three or four years of widespread use and completion of several postmarketing studies, new drugs can be prescribed for children with greater confidence that major, adverse effects are unlikely to be discovered.

Although felbamate is seldom used in the United States at this time, several aspects of its use will be briefly reviewed. It is a broad spectrum antiepileptic agent which appears to be effective in prevention of partial seizures as well as certain forms of generalized seizures. Its mechanism of action is poorly understood. Felbamate is available in scored tablets of 400 and 600 mg and also in a 600 mg/5 ml suspension. It should be divided into 3 daily doses for patients receiving multiple drugs but patients on felbamate alone may sometimes be treated with 2 daily doses. The initial dose is 15 mg/kg/day with subsequent increases to 30 mg/kg/d and 45 mg/kg/d. In my experience, patients seldom achieve better seizure control on 45 mg/kg/d than on 30 mg/kg/d. Headache, insomnia, and anorexia, are the most common complaints in patients receiving felbamate. In obese, adolescent females receiving felbamate as a

substitute for divalproex sodium (which often increases appetite), appetite suppression by felbamate was a side-effect welcomed by the patient. Many patients who found that they were able to lose weight on expressed reluctance to discontinue felbamate and reinitiate their previous medications after the hemotoxicity and hepatotoxicity if felbamate were recognized. Serum felbamate concentrations reportedly have little correlation with seizure control and toxicity, but are potentially valuable for assessing compliance.

Lamotrigine

Lamotrigine is a phenyltriazine deivative whose chemical structure is unrelated to that of other AEDS. It appears to resemble carbamazepine and phenytoin in its mode of action. Lamotrigine inhibits voltage-sensitive sodium channels. This results in stabilization of presynaptic neuronal membranes with the result that release of excitatory neurotransmitters such as glutamate and aspartate is reduced. Although lamotrigine's listed indication is adjunctive therapy for partial seizures in adults (>16 years of age) with epilepsy, a number of articles indicate that the drug is also effective in children with partial and generalized seizures including absence seizures. Lamotrigine is about 55% bound to plasma protein and does not induce cytochrome P-450. It has no significant effect on plasma concentrations of concomitantly administered carbamazepine or phenytoin. Levels of carbamazepine epoxide, a metabolite of carbamazepine, may occur in some individuals. Since carbamazepine epoxide appears to be partially responsible for the neurotoxic effects of carbamazepine, reduction in the carbamazepine dose is sometimes required when lamotrigine is added. Lamotrigire has a mean serum half-life ($T_{1/2}$) of about 25 hours and can be administered twice a day. The $T_{1/2}$ of lamotrigine may increase to 70 hours when lamotrigine is used in conjunction with valproate since the two drugs compete for liver glucuronidation enzymes. Steady state concentrations of valproate fall by an average of 25% over the course of 3 weeks when lamotrigine is added. In add-on trials, approximately one-third of patients receiving lamotrigine, 500 mg per day experienced at least a 50% reduction in seizure frequency. In premarketing and postmarketing clinical trials, about 10% of 357 patients were withdrawn from larnotrigine therapy. Adverse effects leading to withdrawal included rash (3.8%), dizziness (1.3%), headache (1.3%), nausea., ataxia, diplopia, somnolence and blurred vision (each occurring in 0.5 to 0.7% of patients).

In controlled add-on studies, the incidence of rash in patients receiving lamotrigine was 10% and the overall rate of discontinuance because of rash was 3.8%. Rash typically occurs between 2-8 weeks after lamotrigine therapy is initiated. Maculopapular, erythematous rashes are the most common, but life threatening eruptions including Stevens-Johnson syndrome and, rarely, toxic epidermal necrolysis may occur. These rashes may occur as part of a multiorgan hypersensitivity reaction which also includes hepatic and hematologic manifestations. A few deaths have occurred during the course of these reactions. The incidence of serious rashes due to lamotrigine is much higher in pediatric than in adult patients, and there is evidence that the combination of valproate and lamotrigine increases the risk of serious rashes approximately eight-fold. Lamotrigine should only be prescribed in children with intractable seizures and, in most cases, should not be the first of the newer agents which is used. Informed consent is mandatory. When possible, the combination of valproate and lamotrigine should be avoided. The incidence of rashes appears to be reduced by very gradual increase in the dose of lamotrigine. One to two months is usually required to build up the lamotrigine dose sufficiently to improve seizure control. There are very few instances in which it would be appropriate for a general pediatrician to prescribe lamotrigine.

Gabapentin

Gabapentin has many of the attributes of an ideal antiepileptic drug including water solubility, renal elimination, minimal plasma protein binding, minimal interaction with other antiepileptic agents, linear

pharmacokinetics, a low toxicity profile and--at least in animal studies--no teratogenic effects. Although it resembles GABA structurally, it does not appear to affect substantially the availability or metabolism of GABA in the central nervous system. Gabapentin structurally resembles endogenous amino acids, and it acts as a zwitterion at physiological pH. Its pharmacological profile in animal models is distinct from those of older antiepileptic drugs. At clinically relevant concentrations in vitro, gabapentin does not interact with receptors for GABA, benzodiazepines, glutamate, glycine or NMDA (N-methyl-D-aspartate) and it does not appear to directly after sodium or calcium channels. In rats, gabapentin binds with high affinity to a specific site, which is unique to the CNS, throughout brain tissue. This binding site is localized on neuronal cell bodies and is probably associated with the system L neutral amino acid transporter; gabapentin is transported across the gut and probably across the blood-brain barrier and neuronal cell membranes as well by system L. Gabapentin interacts with at least 3 cytosolic enzymes involved with amino acid metabolism: it inhibits branched-chain aminotransferase, which converts L-leucine, L-**isoleucine**, and L-valine into glutaminate, which is an excitatory neurotransmitter. Gabapentin also enhances the action of glutamate dehydrogenase, which catalyzes both the degradation and synthesis of glutamate under certain conditions. It is also a weak inhibitor of GABA transaminase, which degrades GABA into other amino acids. Gabapentin's 3 dimensional structure is similar to that of L-leucine. The observations above suggest that the antiepileptic action of gabapentin results from alterations in the concentration or metabolism of brain amino acids (see Taylor).

Gabapentin listed indication is for adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age. Additional trials are likely to result in a broadening of approved indications; it is likely that gabapentin will be widely used in children and also for monotherapy in patients of all ages. Since it is excreted unchanged in the urine and has no known hepatotoxicity, gabapentin has particular appeal in medically complex patients receiving multiple drugs since in this population avoidance of drug interactions is a major consideration. Because of its freedom from drug interactions and minimal effects on behavior (in the majority of patients), gabapentin may also be useful in psychiatric patients with epilepsy. Gabapentin is widely prescribed for various pain syndromes although this is an off-label indication.

Gabapentin is available in 100, 300 and 400 mg tablets but not as a suspension or a sprinkle. The dose can usually be increased to 300 mg t.i.d. within 3 days, and the listed dose is 300 to 600 mg t.i.d. although larger doses are often used. Because of the drug's short half-life (5-7 hours), steady state plasma concentrations are achieved within 1-3 days on t.i.d. dosing. The most common adverse effects attributable to CNS toxicity: somnolence, dizziness, ataxia, fatigue, nystagmus. These symptoms closely follow initiation of therapy or increase in dose and generally do not persist. There has been at least one report suggesting that gabapentin may exacerbate or precipitate aggressive behavior in children. As is the case with felbamate, serum gabapentin concentrations appear to be of little value in optimizing dosage but may help in verifying compliance.

Topiramate

Topiramate is a structurally unique antiepileptic drug which appears to have multiple modes of action. It is a sulfamate-substituted monosaccharide and appears to prevent seizures by (1) blocking the sodium channels responsible for neuronal depolarization and the generation of action potentials (This is also the major mechanism of action of most of phenytoin and carbamazepine.), (2) enhancing the effect of GABA on $GABA_A$ receptors and thus opening chloride channels to increase the stability of the neuronal membranes, (3) blocking the kainate/AMPA receptor for glutaric acid which is the major excitatory neurotransmitter in the CNS. (4) Topiramate is also a weak carbonic anhydrase inhibitor: this effect is not thought to be a major factor in the drug's antiepileptic activity but may explain a number of its adverse effects. The listed indication for topiramate is adjunctive therapy of partial onset seizures in adults, but, it

has been used for resistant seizures in children and pediatric studies have been reported. Doses up to 9 mg/kg/day have been given. Steady state topiramate concentrations in children were 33% lower than in adults for the same mg/kg dose and reflect greater renal clearance in the pediatric age group. Topiramate has been used as monotherapy in complex partial seizures in children and also shows promise in the "Lennox-Gastaut syndrome." Lennox-Gastaut patients typically have multiple seizure types, which include varyin combinations of atonic, tonic, myoclonic, generalized tonic- clonic, and complex partial episodes.

Adverse effects of topiramate on liver, kidney or bone marrow are rare. Carbonic anhydrase inhibition is probably the cause of paresthesia involving the face or distal extremities in some patients and often occurring 15-30 minutes after medication is taken. Anorexia and weight loss appears to be dose related side effects and occasionally limits therapy. A mild metabolic acidosis has developed in a few of my patients receiving topiramate, and is listed in the manufacturer's prescribing information as a rare adverse effect of topiramate. In my experience, nausea and vomiting occasionally limit use of the drug. CNS effects such as fatigue, nervousness, and attention span difficulties have been reported. Topiramate's function as a glutamate antagonist will undoubtedly lead to a number of studies regarding the effect of the drug on learning and cognition. Excitatory neurotransmitters such as glutamate and glycine are thought to play a role in learning by "allowing the brain's neuronal circuitry to be molded by electrical afferent activity" (M.V. Johnston).

Topiramate has a long half-life and is usually given twice a day. Steady state is reached after about 4 days. Approximately 70% of topiramate is excreted unchanged in the urine. Inactive metabolites are formed in the liver by hydroxylation, hydrolysis, and glucuronidation. Protein binding is approximately 15%. As the above would suggest, topiramate has little effect on the serum concentration of other antiepileptic drugs. A slight increase in phenytoin concentration and a slight reduction in valproate concentration have been reported.

No liquid preparation of topiramate is available. The drug is available in 25, 100 and 200 mg tablets. Adult doses generally range from 400 to 600 mg per day. In adults, the usual starting dose is 50 mg per day, and dosage is increased by 50 mg per week with the result that the full dose is achieved after 8 weeks. In pediatric studies, initial dosage of 1 mg/kg has been used and the dose has been increased by 1 mg/kg/week.

GABA agonists: Tiagabine ant Vigabatrin

GABA (Gamma-aminobutyric acid) is the major inhibitory neurotransmitter in the CNS. $GABA_A$ receptors are found postsynaptically on dendrites as well as on the somatic membrane and axon initial segment. Binding of these receptors by GABA opens the chloride channel and permits ionic flow resulting in hyperpolarization of the cell membrane and transient depression of neuronal activity.

Tiagabine, an antiepileptic agent only recently marketed in the United States, and vigabatrin, which is not yet available in this country, both function as GABA enhancers: Tiagabine inhibits GABA reuptake by presynaptic fibers while vigabatrin increases GABA availability by inhibiting its metabolism by GABA transaminase. GABA itself cannot be transported across the blood brain barrier, but tiagabine, which consists of a nipecotic acid derivative linked to a lipophilic anchor, does cross the blood brain barrier. Although tiagabine is currently listed as indicated for adjunctive therapy in partial-onset seizures in patients over 12 years of age, pediatric studies are in progress and it is likely that the drug will have listed pediatric indications within the next few years. Tiagabine has a relatively short half-life, which may be no more than four hours in patients concomitantly taking enzyme-inducing antiepileptic drugs. However, one study demonstrated benefit even when it was given b.i.d., and this raises the possibility that the

pharmacodynamic effect may be longer than the half-life would predict.

Tiagabine is 96% protein-bound and is metabolized in the liver by cytochrome P450. No active metabolites have been identified. Elimination is linear in healthy subjects, and half-lives are generally 5-8 hours in healthy subjects after single and multiple doses. Since tiagabine does not induce or inhibit hepatic metabolism, it does not alter the concentrations of other antiepileptic drugs with the exception of an occasional small decline in valproate levels. Serious adverse effects of tiagabine on liver, kidney or bone marrow have not been reported, and the drug has no know teratogenic effects although experience during pregnancy is limited. Central nervous system side effects occurring more frequently than in a control group include dizziness, asthenia, nervousness, tremor, and depression.

Tiagabine is available in 4 and 12 mg tablets and is given in 3 daily doses. The adult dose is generally between 48 and 56 mg per day, and it is advised to "start low and go slow" when beginning the drug. The initial dose is 4 mg per day and the dose is increased into the usual therapeutic range over the course of several weeks. In investigational studies, children have received up to 1 mg per kg per day in divided doses.

For an additional comment regarding the use of tiagabine in children, please see the next section.

Vigabatrin

Although not commercially available in the United States, vigabatrin has been widely used in other countries and has been studied in children. In other countries it is considered the drug of choice for infantile spasms. Since tiagabine and vigabatrin are pharmacologically similar, it is likely that trials of tiagabine in infantile spasms will be carried out in the next few years.

Vigabatrin's attributes include a long half-life, minimal protein binding, predominantly renal elimination and a favorable toxicity profile. Note that, although tiagabine and vigabatrin exert their antiepileptic effects through related biochemical pathways, vigabatrin has at least 3 superior pharmacokinetic features: longer half-life, less protein binding, and predominantly renal elimination. The major application of vigabatrin, as is the case with tiagabine, is in the treatment of partial-onset seizures. Vigabatrin may exacerbate some forms of myoclonic seizures (although, as noted above, it may be the drug of choice for "massive myoclonus" or infantile spasms) as well as absences. Vigabatrin may also be helpful in conditions other than epilepsy: tardive dyskinesia may be ameliorated by vigabatrin, and, in a small trial, it was as effective as **baclofen** in reducing spasm and improving other selected manifestations of spasticity in patients with spinal cord lesions or multiple sclerosis. CNS toxicity my occur but is usually mild and may be transient: headache, dizziness, confusion, ataxia diplopia, memory impairment, insomnia each occur in less than 40% of patients. Aggression or overt psychosis occasionally occur and may be more common in patients with a previous history of psychosis. Intramyelinic edema occurred during studies with laboratory animals (not including primates) but has not been observed in epilepsy surgery patients who received vigabatrin preoperatively. Interaction with other antiepileptic drugs is minimal with the exception that phenytoin concentrations may be reduced by 20-30% after vigabatrin is initiated.

New Forms of Old Drugs: Fosphenytoin, Intravenous Valproate, Diazepam Rectal Gel, Oxcarbazepine

In this section are included two drugs which are new although closely related to antiepileptic agents, with which American physicians are already familiar and two which have recently become available.

Fosphenytoin

Fosphenytoin is a phenytoin prodrug which is rapidly converted to phenytoin after intravenous injection. The major advantage of fosphenytoin it is water soluble at a pH of 8.6. By contrast, phenytoin, which is no longer marketed for intravenous use by Parke-Davis but is available in generic form comes in a vehicle containing 40% propylene glycol and 10% alcohol in water adjusted to pH 12 with sodium hydroxide. Intravenous phenytoin carries a risk of severe local irritation, including major sloughs, as well as atrial and ventricular conduction depression and ventricular fibrillation. These risks, are largely eliminated by substitution of fosphenytoin for intravenous phenytoin.

Fosphenytoin can be infused at 2 to 3 times the rate of phenytoin and, as noted above, is much less likely to result in local irritation. In one study, complications or complaints required interruption of phenytoin infusions 67% of the time as compared to 21% for fosphenytoin. These differences may reduce the duration of status epilepticus in some patients receiving fosphenytoin and also carry the potential for reducing emergency room time and use of emergency personnel. Although fosphenytoin is considerably more expensive than intravenous phenytoin, some have argued that the above issues (as well as the medicolegal costs that will undoubtedly be associated with serious complications of intravenous phenytoin in the future) should also be factored into comparative cost benefit analysis

Formic acid and phosphate are metabolites of fosphenytoin. Formate toxicity is similar to methanol toxicity and include metabolic acidosis with a large anion-gap. This might be a consideration in small infants but limited studies suggest that fosphenytoin is well tolerated in small infants. A rapidly deliver, large phosphate load might cause hypocalcemia, manifested by paresthesia, muscle spasms and seizures. Hypocalcemia and severe renal impairment may represent relative contraindications to fosphenytoin administration.

Burning, itching and other paresthesia may occur during fosphenytoin administration and sensory alterations most commonly involve the groin.

Confusing aspects of fosphenytoin use include the brand name and dosage specification. On the one hand, the brand name "Cerebyx: does not help to remind the physician or nurse that the drug is chemically and pharmacologically related to phenytoin (Dilantin). However, presumably to avoid confusion and dosing error the drug must be ordered in "phenytoin equivalents" or PE. The usual loading dose of phenytoin is 10-20 mg/kg, and the loading dose of fosphenytoin is 10-20 mg/kg PE. For a 20 kg child the loading order might be written "Fosphenytoin, 400 mg PE IV over XX minutes." The appropriate rate of administration in children is not specified in the Physician's Desk Reference. In thinking about the rate of infusion for pediatric patients, consider the following: adults receiving a loading dose of phenytoin should receive no more than 50 mg/min. A 50 kg adult would thus receive 20 mg/kg in no less than 20 minutes. The rate of fosphenytoin infusion in adults is 100 to 150 mg PE per minute: a 50 kg adult might receive the entire loading dose in less than 10 minutes. If a child is loaded with phenytoin at the rate of 1 mg/kg/min, a 20 mg/kg loading dose is achieved in 20 minutes. Although phenytoin 50 mg/kg/min may be given to adults, this rate of infusion would be dangerous in a small child and it is safer to give a loading dose at the rate of 0.5 to 1 mg/kg/min (total loading dose administered over 40 to 20 minutes). Similarly, it would not be prudent to load a child with fosphenytoin at the rate of 100 to 150 mg PE per minute. Until prospective studies have been performed, it may be prudent to give fosphenytoin to children at the same rate that one would have chosen for phenytoin: 0.5 to 1 mg/kg/min. Since intravenous fosphenytoin is rapidly converted to phenytoin, there is still a potential risk of cardiovascular complications although this risk is reduced because propylene glycol is not injected with fosphenytoin. Heart rate and rhythm should be monitored during fosphenytoin infusions.

Fosphenytoin can be given IM to patients who have no IV access and are also unable to take oral

phenytoin. Fosphenytoin is supplied in 2 ml and 10 ml vials, each of which contain the drug in a concentration of 50 mg PE/ml. This low concentration reduces the utility of fosphenytoin for MI loading but is certainly consistent with IM maintenance. In a 20 kg child, for example, the loading dose of fosphenytoin might be 400 mg or 8 ml. If a 20 kg child were maintained on oral phenytoin, 5 mg/kg/d in 2 divided doses, substitution of IM fosphenytoin would require injection of 1 ml b.i.d.

Intravenous Valproate

Valproate is now available in intravenous form. This is a convenience for patients who are maintained on oral valproate but are temporarily NPO. Previously, the only related preparation which could be given by a non-oral route was the Depakene capsule, which is liquid filled and can be administered as a suppository. Intravenous valproate also appears to have a role in status epilepticus. A loading dose of 15 mg/kg rapidly produces a serum concentration in the usual therapeutic range. Seizure clusters without status epilepticus may also respond favorably to intravenous valproate. I have had one patient who received intravenous valproate in the emergency room after a series of brief seizures while maintained on another antiepileptic drug despite a serum concentration at the upper end of the usual therapeutic range. Seizures were promptly controlled and the patient was placed on oral valproate. The previous antiepileptic drug was rapidly discontinued. Significant sedation did not occur and admission was not required.

Diazepam Rectal Gel

For years, diazepam suppositories have been available in other countries but not in the United States. American physicians who treat seizures have devised a variety of techniques for rectal administration of the parenteral diazepam preparation. Preprepared syringes of diazepam are now available in a form suitable for rectal administration. Diazepam rectal gel can be ordered in syringes containing 2.5, 5, 10, 15, and 20 mg . Dosage varies by age: 0.5 mg/kg in children 2-5 years of age, 0.3 mg/kg in children from 6-11 years of age and 0.2 mg/kg in children 12 years of age or older. Because rectal diazepam fills a niche market, it is supplied by only a single manufacturer and is expensive.

Now that rectal diazepam is readily available, neurologists and pediatricians must decide who should receive it. Both medical and economic factors undoubtedly will determine the answers to this question. Use of this preparation will undoubtedly be helpful in many children with a history of status epilepticus. Rectal diazoma offers no obvious benefit to most children with infrequent, brief, febrile convulsions unless they occur in clusters. Practical issues such as the distance of the patient from an emergency facility and parental reliability may also influence decisions concerning rectal diazepam.

Oxcarbazepine

CNS toxicity associated with carbamazepine administration may include dizziness, diplopia, nystagmus, and fatigue. These symptoms are attributable, at least in part, to carbamazepine's epoxide metabolites. Oxcarbazepine, which is not yet commercially available, is chemically related to carbamazepine and appears to be equally effective. It is degraded by a different pathway with the result that epoxide metabolites are not produced.

What will be the impact of new antiepileptic drugs on the care of patients with epilepsy? For the 70% of patients whose seizures are readily controlled, the availability of new agents, which will eventually be used as monotherapy, will undoubtedly be helpful in improving the therapeutic index (benefit: adverse effect ratio) during chronic antiepileptic drug therapy. For patients with previously refractory epilepsy, complete or satisfactory seizure control will be probably be achieved in only a minority. Quality of life

studies are necessary to determine when improved seizure control is clinically meaningful in individuals functioning at different levels and at different ages. For example, three brief seizures a month in a quadriplegic five year old may not affect quality of life while one brief seizure a year in an otherwise healthy 17 year old may prevent driving and make an after school job or participation in certain sports impossible.

The availability of antiepileptic drugs, which work by a variety of different mechanisms and which have initially been approved only as add-on therapy, has shifted the trend in epilepsy therapy from monotherapy to "rational polytherapy." These two concepts are not incompatible and will probably guide therapy in different sets of patients.

How will the availability of new antiepileptic agents affect the utilization of neurologists by pediatricians? As a general rule, subspecialty referrals are discouraged in the managed care environment, and the pediatrician is encouraged to manage patients with a variety of chronic disorders including epilepsy. With the advent of new antiepileptic agents, the choice of initial therapy for epilepsy will eventually broaden. It is likely that one or more of the antiepileptic agents discussed above will eventually be used as widely as phenobarbital carbamazepine, phenytoin, or valproate. Most general pediatricians will not have an opportunity to become knowledgeable in the use of more than 2 or 3 antiepileptic drugs. These considerations may justify earlier referral of children with epilepsy.

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